STIC-ILL

ADONIS
#25.00

From: Kwon, Brian-Yong
Sent: Thursday, June 03, 2004 3:24 PM
To: STIC-ILL
Subject: 10/019510

1. "the effect of urocanic acid on graft rejection in an experimental model of orthotopic corneal transplantation in rabbits", Filipec et al., Graefe's Archive for Clinical and Experimental Ophthalmology, 1998, 236(1), 65-68.
2."urocanic acid isomers are good hydroxy radical scavengers: a comparative study with structural analogues and with uric acid", Kammeyer et al., Bichimica et Biophysica Acta, 1999, 1428(1), 117-120.
3. "cis-urocanic acid is not useful as an immunosuppressive agent in the treatment of human allergic contact dermatitis", Kammeyer et all, Archives of dermatological research, 1996, 288 (11), 725-7.

Brian Kwon
REM 4B81
Patent Examiner, Pharm-D.
(571)272-0581

Article title	cis-urocanic acid is not useful as an immunosuppressive agent in the treatment of human allergic contact dermatitis
Article identifier	0340369696001356
Authors	Kammeyer_A Meinardi_M_M_H_M Bos_J_D Teunissen_M_B_M Korstanje_M_J
Journal title	Archives of Dermatological Research
ISSN	0340-3696
Publisher	Springer
Year of publication	1996
Volume	288
Issue	11
Supplement	0
Page range	725-727
Number of pages	3
User name	Adonis
Cost centre	
PCC	$25.00
Date and time	Thursday, June 03, 2004 4:17:09 PM

Arch Dermatol Res (1996) 288 : 725–726

LETTER TO THE EDITOR

Arthur Kammeyer · Marcus M. H. M. Meinardi
Jan D. Bos · Marcel B. M. Teunissen

cis-Urocanic acid is not useful as an immunosuppressive agent in the treatment of human allergic contact dermatitis

Received: 26 January 1996

Key words Immunosuppression · Ultraviolet

Sir,

One of the suggested mediators of ultraviolet-induced immunosuppression is *cis*-urocanic acid (*cis*-UCA), that is formed in the epidermis by photoisomerization of *trans*-urocanic acid (*trans*-UCA) [1]. In animal models *cis*-UCA has shown immunosuppressive effects, including the suppression of both sensitization and elicition of contact allergy. Since *cis*-UCA is a low molecular weight compound (enabling it to penetrate into the skin) it might be an interesting topical agent for therapeutic use in a variety of dermatoses where immunosuppression is needed. With great interest we read the contribution of van Strien and Korstanje [2] who demonstrated a suppressive effect of topical UCA in the treatment of allergic contact dermatitis in human volunteers.

Coincidently, we completed a preliminary study with comparable experiments, using an extended protocol developed earlier for use in the study of the possible efficacy of topical cyclosporin in atopic eczema and allergic contact dermatitis [3]. In brief, patients known to be sensitized to nickel, perubalsam, quinoline mix or fragrances were patch tested with the respective compounds according to a modified ICDRG protocol. We studied the possible efficacy of *cis*-UCA in suppressing the contact allergic response, using *trans*-UCA and vehicle as controls. Patch-test sites were pretreated for 48 h with *cis*- or *trans*-UCA (1% and 0.01% w/v) in 1% carbomer gel (vehicle) prior to the application of allergen, which was present for 72 h under occlusion without the simultaneous application of a UCA isomer.

A. Kammeyer (✉) · M. M. H. M. Meinardi · J. D. Bos
M. B. M. Teunissen
Neurozintuigen Laboratorium, K.2-noord,
Academisch Medisch Centrum, University of Amsterdam,
Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Our results indicated that neither isomer had any effect in preventing elicitation in four individuals sensitized for fragrance mix, perubalsum and quinoline mix. In contrast to the findings of van Strien and Korstanje, we found that only in one out of seven nickel-sensitized individuals did pretreatment with *cis*-UCA moderately suppress the severity of dermatitis. In three out of seven individuals both *cis*- and *trans*-UCA showed moderate suppression of elicitation as compared with control patches treated with vehicle alone. In the three remaining individuals no suppression was found with either UCA isomer. Since the suppressive potential of *trans*-UCA did not substantially differ from *cis*-UCA in this respect, the immunosuppressive capacity ascribed to *cis*-UCA is not very plausible. Unfortunately, van Strien and Korstanje [2] did not include *trans*-UCA as an important control, making it difficult to interpret their results properly. We suggest that both UCA isomers might have functioned as chelating agents for nickel under these conditions. Chelation may prevent the availability of free nickel ions to initiate allergen formation with epidermal macromolecules. To that end, we investigated whether the lack of suppressive ability was caused by inefficient penetration of *cis*-UCA, although it was topically applied in excess. We determined the epidermal concentrations of *cis*- and *trans*-UCA before and after a load of 48 h under occlusion of 1% *cis*- and *trans*-UCA in carbomer gel. Using a filter sampling method and HPLC analysis [1], basic epidermal tissue levels of *cis*- and *trans*-UCA were found to be increased (about eight times) under these conditions, indicating that an effective penetration of UCA isomers in the epidermis of our volunteers had occurred.

To load the epidermis with increased amounts of UCA isomer requires a certain period of time to elapse. We can assume that the application of UCA isomers immediately before the application of the allergen may have the consequence that the migrating allergen is not surrounded by excess *cis*- or *trans*-UCA in the epidermis. In contrast, in our protocol the UCA isomers are present in excess at the time of elicitation and this might favour the study of the

possible suppressive effects of *cis*-UCA and, eventually, *trans*-UCA as well.

We conclude that *cis*-UCA and also *trans*-UCA could suppress some but not all of the elicitation of nickel contact allergic reactions by chelation of nickel ions. Neither *cis*- nor *trans*-UCA are effective in suppressing elicitation responses to other contact allergens. In this respect, neither isomer forms interesting compounds for further development as therapeutic agents in immune-mediated dermatoses.

References

1. Kammeyer A, Petrimissen MBM, Pasel S, De Rie MA, Bos JD (1995) Photoisomerization spectrum of urocanic acid in human skin and in vitro: effects of simulated solar and artificial ultraviolet radiation. Br J Dermatol 132: 884–891
2. van Strien GA, Korstanje MJ (1995) Treatment of contact hypersensitivity with urocanic acid. Arch Dermatol Res 287: 564–566
3. De Rie MA, Meinardi MMHM, Bos JD (1991) Lack of efficacy of topical cyclosporin A in atopic dermatitis and allergic contact dermatitis. Acta Derm Venereol (Stockh) 71: 452–454

Arch Dermatol Res (1996) 288 : 727

REPLY

M. J. Korstanje

Sir,

In animal test models *cis*-urocanic acid (*cis*-UCA) was able to suppress both sensitization and elicitation of contact allergy. In our study and in the study by Kammeyer et al. this effect of *cis*-UCA was studied in humans.

Kammeyer et al. evaluated patch-test areas with a four-point visual nominal scale adopted from the European Contact Dermatitis Research Group, and found no effect of *cis*-UCA. Using this scale we were also unable to detect an effect of UCA. In small populations such as those used in the study by Kammeyer et al. (11 or 18 patients) and in our study (33 volunteers), an inaccurate rough scale like this, is not sophisticated enough to detect any effect other then a very large impressive response. In small populations more accurate and objective methods are necessary for a reliable evaluation of responses. We used laser Doppler flowmetry, which is an accurate and objective method for evaluating patch-test reactions [1]. Using laser Doppler flowmetry we observed a significant reduction in hypersensitivity responses when the skin was pretreated with *cis*-UCA.

A vehicle, which is applied to the skin prior to the application of an allergen, may reduce the penetration of the allergen in the skin. We used a 60% ethanol solution, which most likely does not reduce the penetration of the allergens. We do not know whether the carbomer gel used by Kammeyer et al. reduced the skin penetration of the allergens applied. Further, as Kammeyer suggested, it may be possible that UCA functions as a chelating agent for, e.g., nickel.

Both studies are small and prone to type I and type II statistical errors. Larger studies are warranted before *cis*-UCA could be used in the preventive treatment of contact hypersensitivity responses.

M. J. Korstanje
Irislaan 28, 5595 EH Leende, The Netherlands

Reference

1. Li Q, Aoyama K, Matsushita T (1992) Evaluation of contact allergy to chemicals using laser Doppler flowmetry (LDF) technique. Contact Dermatitis 26 : 27–33